The present invention relates to administering to a host a cancer metastasis inhibiting amount of a synergistically amount of N-acetyl-cysteine (NAC) and Doxorubicin (DOX).

The Myers et al. reference (U.S. Patent No. 4,331,648) relates to the treatment of tumors with a combination of NAC and DOX. N-acetyl-cysteine prevents cardiac damage occurring after administering anthracycline. No effect regarding the antitumoral activity is reported for NAC, and in this connection, see column 3, lines 48-52, which states "these experiments demonstrate that N-acetyl-cysteine does not in and of itself possess antitumor properties and it does not interfere with doxorubicin's ability to treat sensitive P388 ascites tumor".

From the above it is certain that Myers et al. is not reporting a synergistic effect between NAC and DOX as in the claimed invention, and in fact teaches away from a synergistic effect.

The Doroshow et al. reference is more or less equivalent to the Myers patent. Again, at page 1060 of this document, the authors report "these results suggest that a dose of NAC (2000 mg/kg) that ablates electron microscopic evidence of doxorubicin cardiac toxicity does not interfere with the drugs antitumor activity against P388 leukemia".

Myers et al. (Seminars in Oncology) relates to the Doroshow publication. This reference reports the results of a trial for evaluating the effect of NAC in protecting against chronic cardiomyopathy that may be associated with DOX. Specifically, in the chapter under thw heading entitled *Effective NAC on Tumor Response* it is reported " while this trial is not designed to evaluate the impact of NAC on tumor response... [t]he percentage of patients with stable disease plus those with partial transmission in the two arms was 33% for DOX alone and for 50% DOX plus NAC. Because of the diversity

of tumor types involved, no statistical analysis of this difference was attempted". Furthermore, under the heading entitled conclusions, the authors are rather discouraging regarding the efficacy of NAC treatment. There is no disclosure of a synergistic effect of using combinations of NAC and DOX in the inhabitation of *metastasis formation.*

The reference to Freeman et al. is really the only pertinent reference to the present invention. This is so because it relates to the study of the effect of sulphur compounds (e.g. NAC) on antitumor affects of adriamycin. However, the last sentence of the abstract states "the mechanism of sulphydryl-induced protection against the cardiotoxicity of ADR appears not to interfere with the antitumor activity of ADR.".

Again, the prior art reference teaches away from a synergistic effect as taught in the present invention.

The rejection of claims 10-12 under 35 USC §102 as being anticipated by Meyers et al. (Seminars in Oncology) is respectfully traversed. This reference is discussed in daertail above. It does not disclose a synergistic effect between NAC and Dox in *metastasis formation.*

The rejection of claims 10 and 12 under 35 USC §102(b) as being anticipated by Mayhew (U.S. Patent 4,873,088) is respectfully traversed.

Mayhew merely confirms the well known activity of NAC in protecting against a cardiac side effect of adriamycin. The patent relates to a lithosone composition useful for the administration of adriamycin and includes also the use of a known protective (i.e., having the ability to reduce toxicity) agent in the composition. There is no disclosure of synergistic affect of using NAC and DOX in stemming tumoral activity.

The rejection of claim 10 under 35 USC §102 as being anticipated by Imamura et al. (Cancer Research) or Kiang et al. (Minnesota Medical Association) is respectively traversed.

Imamura et al. describes that NAC is able to antagonize the negative affects of adriamycin. In particular, it describes that NAC partially inhibits the considerable increment of the invasive capacity of rat ascites hepatoma cells observed with adriamycin treatment. Once again, the disclosure is deficient. It does not describe or disclose a synergistic affect between the use of NAC and DOX against tumoral activity. The reference merely relates to a demonstration that adriamycin is a toxic compound and that NAC is able to protect against toxicity.

The Kiang et al. reference confirms that NAC is a useful protective agent against cardiac damage related to administration of adriamycin.

Once again, the claimed invention relates to treating host having tumors with synergistic combinations of NAC and DOX. It is clear that none of the prior art discloses such effects despite the enormous documentation in this art and studies of these compounds, nobody has observed any synergistic antitumoral affect of the two drugs except for the present Applicants.

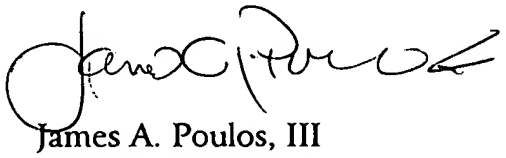
Therefore, Applicants respectfully submit that this application is now in condition for allowance. In view of the forgoing, Applicants respectfully solicit a Notice of Allowance.

If for any reason the Examiner feels that the application is not now in condition for allowance, it is respectfully requested that the Examiner contacts, by telephone, the applicant's undersigned attorney at the indicated telephone number to arrange for an interview to expedite the disposition of this case.

The Commissioner is authorized to charge payment for any additional fees which may be required with respect to this paper to our Deposit Account No. 14-1060.

Respectfully submitted,

NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP



James A. Poulos, III
Attorney for Applicant
Registration No. 31,714

Attorney Docket No. P8903-8035

Metropolitan Square
655 15th Street, N.W.
Suite 330 - G Street Lobby
Washington, D.C. 20005-5701
(202) 638-5000

POU/gw
Attachment: Petition for Extension of Time